NATIONAL OSTEOPOROSIS FOUNDATION

Fighting Osteoporosis & Promoting Bone Health

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Dr. David Orloff
Director
Division of Metabolic and Endocrine Drug Products
Food and Drug Administration
14B45
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Orloff:

As President of the National Osteoporosis Foundation (NOF), I am responding to the Food and Drug Administration's (FDA) requests for comments regarding the Draft Guidance for Industry on the Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis; Docket No. 2004D-0035, CDER 2003158.

The NOF is the leading national voluntary health organization solely dedicated to promoting lifelong bone health in order to reduce the widespread prevalence of osteoporosis and associated fractures, while working to find a cure for the disease through programs of research, education and advocacy. Osteoporosis and low bone density pose a major public health risk for an estimated 44 million Americans. In the US today, 10 million individuals are estimated to already have the disease and almost 34 million more are estimated to have low bone mass, placing them at increased risk for osteoporosis.

The original Guidance document from 1994 provided the critical requirement that agents proposed for the treatment of osteoporosis show reductions in fracture risk. Clinical trials with several anti-resorptive agents, and more recently with anabolic agents, have been conducted using randomized, placebo-controlled designs that were powered to show fracture risk reductions. Since 1995, physicians who treat patients with osteoporosis and the patients themselves have been fortunate to have these new, safe and effective therapies made available to them. Clearly, however, the search for effective and safe treatments is far from over. We can now reduce the risk for low trauma fractures in a clinically meaningful way, but we have neither eliminated the risk of fragility fractures nor have we cured the disease. Continuing research in bone biology will lead to the development of new

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compounds and devices to be tested, and there are compelling social and economic factors that will require the evolution of newer and better approaches to managing this major public health problem. It is ironic that the very success we have achieved to date will make the designs of the clinical trials that will study new agents much more of a problem for pharmaceutical company sponsors, for clinical investigators and for patients.

FDA asks for comment on the question of whether it is appropriate, both ethically and scientifically, to continue to use placebo controls in fracture end point trials. As you are aware, this question was debated at a meeting sponsored by American Society for Bone and Mineral Research in 2002 and more recently by FDA at its own hearing. Many members of the scientific community believe that it is ethically impermissible to use placebo controls in fracture end-point trials with high risk patients. Placebo controlled studies involving fully informed lower risk subjects, e.g. those with less severe low bone mass and an absence of prior fractures, may be ethically possible, but would require very large numbers of participants for relatively long periods of time to be able to have a fracture end point. Active comparator and non-inferiority studies solve some of the ethical problems, but may be less satisfactory in terms of arriving at scientifically complete answers. Industry must be motivated to commit the resources needed to conduct large, long-term studies. The entire question of whether fracture end points are still required (part of your second question) is a very complicated one. It requires a careful evaluation of the current evidence and the validity of using pre-clinical data and novel methods for assessing bone quality and quantity in the clinical trial subjects in order to be addressed.

All of us, together with the FDA, are struggling to resolve this difficult dilemma. Previous meetings to debate the issues have delineated the arguments but have not been required to result in specific recommendations. We believe that a revision of the guidance may indeed be needed in order to take advantage of new science to develop new agents, to protect the rights of subjects, to make it possible for pharmaceutical companies to engage in the process without massive costs that ultimately would be passed on to consumers, and to result in medications that are clearly safe and effective.

Therefore, NOF wishes to encourage the FDA to convene a two day meeting at which basic scientists, clinical investigators and clinicians from academia, industry and clinical care settings, as well as ethicists, statisticians, representatives from IRBs and members of the public who have an interest in osteoporosis can raise and debate the issues before an FDA Advisory Panel and representatives from FDA. After the relevant issues derived from your two questions are presented and reviewed, you could pose additional questions to the panel, seeking guidance on how to proceed. Previous meetings on this topic have discussed the issues and not reached conclusions,

but this meeting would need to end with specific recommendations on how to proceed with altering or maintaining the current guidance.

If you choose to hold such a hearing, NOF would be happy to work with you to assist in the development of the topics and the identification of possible speakers, in an effort to help you reach the best possible solution to this critical problem. The design of clinical trials for testing promising new therapies for osteoporosis is one of the most important issues facing all of us who work each day in so many different ways to help patients who are at risk for osteoporotic fractures. We commend you for the serious effort you are making to resolve the dilemma we face, and offer you our support and help as we address these challenging questions.

Sincerely,

Bess Dawson-Hughes

Bess Dawson-Hughes, M.D
President

Cc: Dr. Lester Crawford
Acting Commissioner